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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/316,935	05/22/99	MELIEF	C 98-4

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EXAMINER	
BECKERLEG, A	
ART UNIT	**PAPER NUMBER**
1632	8

DATE MAILED: 10/04/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

File

Office Action Summary

Application No.	Applicant(s)
09/316,935	Melief et al.
Examiner	**Group Art Unit**
Anne Marie S. Beckerleg	1632

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-13 is/are pending in the application.

Of the above, claim(s) 8-13 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-7 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892 ✓

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 4,7 ✓ ✓

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948 ✓

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Election/Restriction

Applicant's election with traverse of Group II, claims 1-7, wherein the CD40 binding molecule is an antibody, by telephone interview between Eric Mirabez and Eleanor Sorbello on 1/27/00 is acknowledged. As applicant's have not supplied any arguments in response to the grounds of restriction, this restriction requirement is **maintained** and made **final**. This application contains claims 8-13 drawn to an invention nonelected with traverse. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claims 1-7 are active in the instant application. An action on the merits follows.

Nucleic acid and amino acid sequences

The specification discloses three amino acid sequences which are annotated as SEQ ID NOS: 1-3. Applicant's paper copy of the sequence listing and CRF only list two sequences SEQ ID NOS: 1-2. A complete sequence listing including SEQ ID NO. 3 and corrected CRF are required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, and 5-7 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification discloses a pharmaceutical composition comprising a CTL activating peptide and an anti-CD40 antibody. The specification does not disclose or provide any written description for any CTL activating peptides other than SEQ ID NO. 2 and SEQ ID NO. 3. The specification does not identify proteins which may contain CTL activating peptides, or describe any physical or chemical characteristic of peptides which are CTL activating *in vivo* which could be used to identify or isolate candidate CTL activating peptides. Thus, of the enormous number of possible amino acid sequences encompassed by the claims, the specification lacks written description for the identity and the amino acid sequences of any peptides other than SEQ ID NOS: 2 and 3 which are in fact CTL activating. *Vas-Cath Inc. V. Mahurkar,* 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art

that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of 'written description' inquiry, whatever is claimed" (see page 1117). By failing to identify or describe any CTL activating peptides other than SEQ ID NOS. 2 and 3, the specification does not "clearly allow persons or ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). Adequate written description requires more than a mere statement that an element is part of the invention. The sequence itself is required. Based on the applicant's specification, the skilled artisan cannot envision the detailed chemical structure of the encompassed peptide epitopes that are CTL activating and which have are capable of having a therapeutic effect *in vivo,* therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. See *Fiers v. Revel,* 25 USPQ2d 1602 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision.

Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for pharmaceutical compositions comprising a monoclonal antibody directed against CD40 and the HPV16 E7 peptide having the sequence of SEQ ID NO. 3 suspended in IFA, and methods of reducing tumor growth of an E7 expressing tumor by subcutaneously administering the pharmaceutical composition wherein the anti-CD40 antibody is species matched to the recipient, does not reasonably provide enablement for pharmaceutical compositions

comprising any CTL activating peptide or the use of said compositions to treat any tumor or infectious disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. The specification discloses the treatment of infectious disease or tumors by administering a pharmaceutical composition comprising a CTL activating peptide and a CD40 binding protein which is an antibody. It is noted that the specification clearly identifies the use of the disclosed pharmaceutical compositions to treat disease, particularly cancer.

The specification does not provide an enabling disclosure for identifying CTL activating peptides useful in a pharmaceutical composition for treating any tumor or any infectious disease. The specification only discloses two peptide epitopes, the adenovirus-derived E1A peptide having the sequence of SEQ ID NO. 2 and the HPV16 E7 peptide having the sequence of SEQ ID NO. 3. The specification neither discloses nor makes specific reference to the sequence or characteristics of any other peptide that is capable of activating CTL. The specification provides no guidance concerning the characteristics of CTL activating peptides, such as the length, amino acid composition, hydrophobicity, and stability under physiological conditions. Further, the specification does not provide methods for identifying and obtaining CTL activating peptides from any and all proteins such as infectious disease antigens or antigens associated with tumors. While SEQ ID NO 2 and SEQ ID NO 3 are derived from viral proteins, the specification does not teach which characteristics of these sequences is responsible for their CTL activating activity. This issue is further complicated by the fact the E1A peptide having SEQ ID NO. 2 does not have CTL

activating activity in the absence of anti-CD40. Thus, in addition to failing to provide guidance as to which peptides have CTL activating activity in and of themselves, the specification provides no guidance as to identifying characteristics of peptides which would acquire CTL activating activity in the presence of anti-CD40 antibody. Furthermore, the specification fails to provide any guidance for identifying CTL activating peptides which have any pharmaceutical activity *in vivo* and which can be used to treat tumors or an infectious disease. It is noted that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. In re Goodman, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing In re Vaeck, 20 USPQ2d at 1445 (Fed. Cir. 1991). Further, 35 U.S.C. § 112 requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. In re Fisher, 166 USPQ 18, 24 (CCPA 1970). In addition, the Federal Circuit has stated that:

> ..a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, **when there is no disclosure** of any specific starting material or **of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art**. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. Genentech Inc. v. Novo Nordisk A/S, 42 USPQ2d 1005 (CAFC 1997) (emphasis added).

Thus, in view of the specification's lack of guidance concerning identifying or using any CTL activating peptide other than SEQ ID NOS:2 and 3 in pharmaceutical compositions comprising a CTL activating peptide and an anti-CD40 antibody and the breadth of the claims, it would have required undue experimentation to practice the scope of the instant invention as claimed.

The specification does not provide an enabling disclosure for treating any tumor or infectious disease by administering a composition comprising any CTL activating peptide and any anti-CD40 antibody using any route of administration other than the combination of the HPV16 E7 peptide (SEQ ID NO.3) suspended in IFA and a species specific anti-CD40 antibody for the treatment of an E7 expressing tumor. The two CTL activating peptides described by the specification each comprise a single MHC class I epitope. The potential immune response to vaccination with a single MHC class I epitope is limited to a CTL response as the epitopes described do not bind to MHC class II. While low affinity antibodies might be generated by the peptides, it is unlikely that such antibodies would recognize the parent protein in view of protein folding and conformation. In terms of generating a therapeutic CTL response, the specification does not provide sufficient guidance as to the level of CTL response against a single peptide epitope which correlates with protection against any type of infection or against tumor growth and development. The specification does not specifically identify any infectious diseases which can be treated using the instant methods or identify infections which can be successfully treated by generating a CTL response alone. Further, the specification does not provide sufficient guidance as to the affects of the route of administration on CTL generation or demonstrate that injection of

peptide and anti-CD40 either systemically or locally at any site in the body can generate therapeutic CTL activity.

The specification provides a working example which demonstrates that the subcutaneous administration of a peptide having SEQ ID NO. 3 derived from HPV16 E7 suspended in IFA and a murine anti-CD40 antibody to mice results in an anti-E7 CTL response. However, this data is not shown. The example also demonstrates increased survival following challenge with an E7 expressing tumor in mice vaccinated with the SEQ ID NO. 3 peptide in IFA and anti-CD40. As the specification does not provide controls wherein the peptide is administered in the absence of adjuvant (IFA), it is unclear whether the presence of adjuvant is critical to the generation of the observed CTL response as adjuvant, even incomplete Freund's adjuvant, results in non-specific immune activation. Further, it is noted that the example utilizes a species matched anti-CD40 antibody. It was well known at the time of filing that the administration of xenogeneic proteins, such as antibodies, results in an immune response against the foreign protein. In view of the strong immune response against xeno-antigens, the skilled artisan would not be able to predict whether a xeno-anti-CD40 antibody would persist in sufficient quantity in a patient to have any effect on peptide specific CTL generation.

The specification also provides a working example which demonstrates that the subcutaneous administration of the peptide having SEQ ID NO. 2 derived from Adenovirus E1A protein suspended in IFA and a murine monoclonal anti-CD40 antibody to mice resulted in peptide specific CTL generation. In the absence of the anti-CD40 antibody, the administration of

the peptide in IFA alone tolerized the mice to CTL generation. While this example demonstrates the generation of a CTL response, it fails to correlate the observed level of peptide specific CTL activity as measured *in vitro* with any effect on any infection or tumor *in vivo*. At the time of filing, the literature teaches that the strength and character of an immune response to a particular antigen significantly effects the efficacy of that immune response to treat disease symptoms. As a result, even a strong CTL response may be insufficient to treat an infection in the absence of a humoral response. For example, Yasutomi et al. teaches that immunization of rhesus monkeys with a live viral vector which encodes the SIV gag protein generate a non-protective CTL response, but fails to generate a humoral immune response despite the presence of MHC class II and antibody binding epitopes in the gag protein (Yasutomi et al. (1995) J. Virol., Vol. 69 (4), page 2279, abstract). In addition, Yasumtomi et al. teaches that while boosting vaccinated animals with a gag peptide/liposome complex significantly increases the anti-gag CTL response, it still did not provide increased protection against SIV challenge (Yasumtomi et al., *supra*, abstract). The situation is even more complicated in the case of raising therapeutic immune responses against tumors. In order for a cytolytic T cell to kill a target tumor cell, the tumor cell must be presenting sufficient amounts of specific peptide/MHC class I complexes on the cell surface. The literature teaches that tumors evade immune response by a variety of mechanisms including loss of antigenic epitopes by either lack of expression or mutations, loss of functional β_2m expression or of particular MHC class I alleles, and down-regulation of putative antigen processing molecules, including TAP and MHC-encoded proteosome components (Restifo et al (1993) J. Immunother.,

Vol. 14, page 183, col 1, lines 8-14, and page 184, col. 2). Therefore, in the absence of guidance from the specification as to the level of CTL generation against a peptide epitope which is sufficient to treat any neoplastic disease or infection in the absence of a humoral response, the art recognized unpredictability of protecting against infection based on a CTL response alone, and the difficulties involved in immune recognition of tumors, and the breadth of the claims, the skilled artisan would not have predicted success in treating any tumor or infection by administering any CTL activating peptide in combination with an anti-CD40 antibody.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 4 recites an E1A peptide having the sequence SGPSNTPPEI (SEQ ID NO.1). However, the specification and sequence listing both disclose that SEQ ID NO. 1 has the sequence VNIRNCCYI. Clarification is requested.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Feltkamp et al. (1993) Eur. J. Immunol., Vol. 23, 2242-2249 in view of WO 96/26735 (Alderson et al.) Sept. 6, 1996. The applicant claims pharmaceutical compositions comprising a CTL activating peptide and a CD40 binding molecule which is an antibody. The applicant further claims said composition wherein the anti-CD40 antibody is human or wherein the CTL activating peptide is the HPV16 E7 peptide having the sequence RAHYNIVTF. In addition, the applicant claims the use of said compositions for the treatment of tumors.

Alderson et al. teaches the stimulation of anti-tumor immune responses by administering an anti-CD40 antibody, preferably a human monoclonal anti-CD40 antibody (Anderson et al., pages 5, 19, and 21, particularly claims 9 and 21-22). Feltkamp et al. teaches the stimulation of anti-tumor immune responses against HPV expressing tumors by administering an HPV E7 CTL

peptide epitope, and specifically discloses the use of the epitope RAHYNIVTF to immunize mice against tumor challenge (Feltkamp et al., page 2242, abstract, and page 2246, Table 3). While neither Feltkamp et al. nor Armitage et al. expressly teaches the combination of E7 peptide and anti-CD40 antibody to treat cancer, the instant situation is amenable to the type of analysis set forth in In re Kerkhoven, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to produce a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. Given the teaching of the prior art compositions of E7 peptides and anti-CD40 antibodies as pharmaceutical compositions for the treatment of cancer, it would have been *prima facie* obvious to one of ordinary skill in the art to combine these compositions to generate a new composition for the treatment of cancer with a reasonable expectation of success.

In regards to the direct administration of a composition comprising a CTL activating peptide and an anti-CD40 antibody to the tumor itself, the skilled artisan would have been motivated to use intratumoral injection of the composition of peptide and antibody in order to concentrate the ensuing immune response at the site of the tumor itself. Intratumoral injection of pharmaceutical compositions was a well known technique at the time of filing. As such, it would have been *prima facie* obvious to the skilled artisan to utilize intratumoral injection of a composition of CTL activating peptide and anti-CD40 antibody and the skilled artisan would have had a reasonable expectation of success in treating cancer using this route of administration.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne Marie S. Beckerleg, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Thurs and every other Friday from 8:30-6:00. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The official fax number is (703) 308-4242.

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